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External physical and biochemical stimulation to enhance skeletal muscle bioengineering☆

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ABSTRACT

Purpose of review: Cell based muscle tissue engineering carries the potential to revert the functional loss of muscle tissue caused by disease and trauma. Although muscle tissue can be bioengineered using various precursor cells, major limitations still remain.
Recent findings: In the last decades several cellular pathways playing a crucial role in muscle tissue regeneration have been described. These pathways can be influenced by external stimuli and they not only orchestrate the regenerative process after physiologic wear and muscle trauma, but also play an important part in aging and maintaining the stem cell niche, which is required to maintain long-term muscle function.
Summary: In this review article we will highlight possible new avenues using external physical and biochemical stimulation in order to optimize muscle bioengineering.

Contents

1. Introduction

The loss of contractile muscle tissue remains to be a major medical problem, since systemic muscle disease and localized muscle damage cause significant loss in quality of life of affected patients. Urinary incontinence caused by damage to the sphincter muscle is one of the major clinical challenges in urology of the 21st century [1]. The most common form of incontinence is stress urinary incontinence due to muscle and nerve damage resulting from vaginal delivery, aging or tumor therapy [2]. With a growing elderly population and an increased number of men treated for prostate cancer, new therapeutic approaches for continence recovery are needed. Current treatment options include pelvic floor muscle training, pharmacological treatments, or surgical intervention [3]. The long-term efficacy of these options is often not satisfying and they are associated with a number of possible side effects [4].

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The replacement of the damaged sphincter muscle with engineered muscle tissue for functional recovery is proposed as a new treatment option with little or no side effects. Cells currently investigated for use in regeneration of the sphincter muscle are committed muscle satellite cells [5–8] and adult stem cells, including skeletal muscle derived stem cells (MDSCs) [9], bone marrow mesenchymal [10], and adipose-derived stem cells (ADSCs) [11,12]. Promising results were achieved with satellite cells or muscle precursor cells, which have been widely investigated for muscle regeneration for a variety of genetic and acquired muscle disorders [8,13–15].

The term "satellite cell" linked with muscle tissue was first used in 1961 by Alexander Mauro, who observed a group of mononucleated cells at the periphery of adult skeletal muscle myofibers by electron microscopy [16]. Already in this first report Mauro suggested an involvement of these cells in muscle growth and regeneration. In the following years scientific evidence confirmed the mitotic activity [17] and its rapid activation following muscle injury [18]. After tracking the satellite cells during the next steps of muscle regeneration a map of myogenesis could be drawn; satellite cells showed transformation to myoblasts [18] which in turn would form myotubes [19]. They not only showed the ability to give rise to myoblasts, they were also capable of self-renewal through asymmetric and symmetric division [20]. Satellite cells are postnatal stem cells, exclusively dedicated to the formation of myotubes. Based on this observation, satellite cells are also referred to as muscle precursor cells (MPCs) more recently.

The process of muscle regeneration through MPCs has been subject to extensive research over the last years, with the aim to not only understand the physiology, but to also develop strategies to influence proliferation and differentiation in experimental and clinical settings. We currently understand that this process is primarily driven by growth factors, which are altered by tissue injury or exercise [21,22]. Predisposing factors for the outcome of the subsequent regeneration are intactness of innervation, extent of vasculature, hormones and nutrition [23]. This dynamic interplay between MPCs and their environment, often referred to as niche, plays a crucial role in their utilization in regenerative medicine.

Regenerative medicine aims to learn from natural processes and to apply these established strategies to comply with all of the demands of MPCs during regeneration and growth, in order to ultimately engineer a tissue resembling functional muscle. However, a complex interplay of soluble factors, metabolic optimization and biophysical stimulation will be needed to optimize muscle fiber regeneration. Depending on the nature of the approach, these factors can be applied in different chronologies; cells can be treated in vitro before or during implantation. Regeneration can also be enhanced in vivo after implantation. Unfortunately, the full potential of these technologies has not been realized today.

The goal of this review is to highlight possible pathways to improved muscle tissue engineering for clinical application by evaluating the physiologic and pathologic cellular changes in muscle wasting and regeneration. It can reasonably be assumed, that the ideal protocol will consist of a combination of different strategies.

2. Metabolic optimization

2.1. Muscle fiber types

Plasticity of skeletal muscle is facilitated by adaptations of the metabolic and contractile fiber type [24]. In rodents, slow-twitch, high endurance type I and IIa fibers are clearly distinct from fast-twitch, high peak force type IIx and IIb muscle fibers [25]. In humans, the fiber types are restricted to type I, IIa and IIx, and a number of hybrid fiber types [25]. Defined neuronal activation patterns dominantly regulate the metabolic and myofibrillar properties of muscle fibers [26]. For example, continuous motor neuron firing, resulting in low-amplitude intramyocellular calcium levels, promotes a slow-twitch fiber type [26]. Inversely, a sporadic motor neuron activation linked to the high amplitude of sarcoplasmic calcium spikes favors the expression of a fast-twitch fiber-specific gene program [26]. In both cases, clearly distinct paradigms of physical activity underlie the differential motor neuron activation. Thus, endurance and resistance training are associated with a switch towards a higher proportion of slow- and fast-twitch muscle fibers, respectively. Importantly, the phenotype of the muscle fibers by far exceeds the obvious difference in the contraction kinetics. On one hand, slow-twitch muscle fibers mostly use oxidative metabolism of glucose, lipids and lactate to synthesize ATP for long, sustained contractions [25]. Moreover, a pronounced tissue vascularization, elevated myoglobin levels and improved import mechanisms for these three energy substrates all contribute to the high endurance phenotype of these fibers [25]. Finally, a cell-autonomous remodeling of intramyocellular calcium handling and the neuromuscular junction ensure a persistent switch in the fiber type [25]. Most strikingly however, slow-twitch muscle fibers exhibit a massive proliferation of both intramyofibrillar as well as subsarcolemmal mitochondria concomitant with a corresponding boost in mitochondrial function. The increase in heme-containing proteins, e.g. many of the respiratory chain proteins, and the pronounced tissue vascularization confer the typical red color to the oxidative muscle beds with a high number of slow-twitch muscle fibers [25]. In contrast, muscles with a high proportion of fast-twitch muscle fibers appear more whitish. These fibers primarily rely on anaerobic glycolysis to generate the ATP required for fast-twitch contractions with a high peak force [25]. Accordingly, this type of contraction cannot be sustained for a prolonged time and hence, fast-twitch fibers exhibit a higher fatigability compared to slow-twitch muscle fibers. Moreover, due to the predominant dependence on anaerobic metabolism of glucose, fast-twitch muscle fibers are low on mitochondria in terms of number and activity. Importantly however, fast-twitch muscle fibers have a high potential to undergo hypertrophy: the increase in fiber, and therefore also of the muscle cross-sectional area, allows the synthesis and deployment of additional contractile elements and as a consequence, an increase in peak force [25]. Hypertrophy in these fibers is mainly driven by a shift in the balance between protein synthesis and degradation, favoring the former process [27].

2.2. Molecular regulation of muscle plasticity

Surprisingly, the underlying molecular mechanism that differentiates between the fast- and slow-fiber type programs is unknown. In particular, the machinery that interprets the different calcium transients in fast- vs. slow-twitch muscle fibers remains largely elusive. Nevertheless, several important key players for the metabolic and myofibrillar adaptations in either direction have been identified. In slow muscle fibers, the calcium/calmodulin-dependent protein kinase (CaMK) and the protein phosphatase calcineurin A (CnA) are intimately involved in the calcium-dependent signaling cascade resulting in the oxidative, high endurance program [26]. Various sensors of the altered metabolic demands in these muscle fibers furthermore promote the same phenotype [28]. For example, a shift in the ratio between intracellular AMP and ATP leads to an activation of the AMP-dependent protein kinase (AMPK). Similarly, the relative levels of NAD+ and NADH determine the activity of the protein deacetylase sirtuin 1 (SIRT1) in a catabolic context. Inversely, high substrate levels lead to the activation of the mammalian target of rapamycin (mTOR)- and protein kinase B (PKB/Akt)-controlled signaling pathway, that promotes protein biosynthesis and other anabolic pathways [27]. In contrast, myostatin-signaling through activin receptors, in particular type IIB (ActRIIB), limits growth of muscle mass [27]. The neuroendocrine milieu during and after exercise also result in muscle adaptations, in particular by catecholamine-signaling via β2-adrenergic receptors, glucocorticoid and thyroid hormone signaling through the nuclear glucocorticoid receptor and the thyroid hormone receptor [28], respectively, or the adipokines adiponectin and leptin [29]. The mechanical stress in a